REMARKS

Claims 23, 24, 26 and 28-37 have been examined in the present application. Applicants cancel without prejudice, claims 1-22 as being drawn to a non-elected invention subsequent to the Examiner's final decision regarding restriction of the claims in the present application. It is noted that Applicants reserve the right to continue prosecution of the subject matter encompassed by the canceled claims in a related copending application. Further, Applicants have amended claim 23 to set forth the invention with greater particularity as further detailed below. All amendments to the claims are supported by the specification as filed and no new matter has been added. Applicants respectfully request reconsideration of the pending claims in view of the amendments above and the below remarks.

Rejections Under 35 U.S.C. § 112:

Claims 23, 24, 26 and 28-37 stand rejected under 35 U.S.C. § 112, second paragraph, the Examiner remaining convinced that the phrase "directly isolated" is confusing. Further, the Examiner believes that the claims are indefinite because "it is not clear which cell population is directly isolated from peripheral blood, i.e., is it a population of B cells?" In addition, the Examiner does not believe that the property of "directly isolated from peripheral blood" can be used to distinguish the two populations, because the claimed population of dendritic cells seems to be taken directly from peripheral blood for centrifugation. Also, the Examiner appears to believe that an indication comparing the volume from which the populations of dendritic cells have been obtained is required.

Although Applicants believe claims 23, 24, 26 and 28-37 are sufficiently defined as required under 35 U.S.C. § 112, second paragraph, claim 23 has been amended in order to further expedite prosecution of certain aspects of the claimed invention. In particular, the phrase "directly isolated " has been deleted. Further, as stated previously the two cell populations do not differ in any way except that the cell population of the

present invention has been contacted *in vitro* with a prostate antigen. Contact with the prostate antigen allows dendritic cell precursors present in the cell population to uptake and process prostate antigen and to complete maturation. The claimed cell population comprises an increased number of dendritic cells competent and able to activate T cells specific to the prostate antigen than the cell population that has not been contacted *in vitro* to the prostate antigen. This amendment is fully supported by the specification as filed and further is made without prejudice to continued prosecution of any subject matter believed to be withdrawn in a related co-pending application.

Rejections Under 35 U.S.C. § 102:

Claims 23, 24 and 31-36 remain rejected under 35 U.S.C. § 102 as anticipated by Cohen *et al.*, the Examiner believing the rejection to be evidenced by Sallusto *et al.*, Koch *et al.*, and Czernieki *et al.* for the reasons of record in paper no. 19. Further, the Examiner has acknowledged Applicants recitation of Zhou *et al.* and Koski *et al.* discussed in an interview conducted February 27, 2002 between the undersigned representative of Applicants, an employee of the Assignee, and the Examiner. During the interview certain characteristics of mature dendritic cells were discussed including the expression of the cell surface marker CD83 on the surface of mature DCs and the inefficient processing of antigen characteristic of mature DCs expressing CD83. The rapid appearance of many of the characteristic of mature DCs by human blood monocytes and DCs treated with calcium ionophore (within 4 to 18 hrs; Koski *et al.*) was also discussed. Further, Applicants discussed with the Examiner the speculative nature of Example 2 of Cohen and that the dendritic cells subsequent to calcium ionophore treatment were mature dendritic cells and incapable of efficiently processing antigen.

In the present final rejection, the Examiner has reevaluated her position at the close of the interview and has now concluded that "Koski *et al.* teach that monocyte CD83 expression appears within 4 hrs and peaked at 20 hours of calcium ionophore treatment, whereas with a combination of cytokine treatment CD83 expression is seldom observed before 5 to 7 days of culture." From these data presented in Koski *et al.* (pg.

10, first column, first paragraph) the Examiner has now determined that "one would have expected that monocytes treated with calcium ionophore would have immature dendritic cells that are able to activate T cells specific to a prostate antigen, provided the treatment with calcium ionophore is not prolonged, and the treated monocytes are used within 20 hours and preferably within 4 hours after the initial treatment with calcium ionophore." Still further, the Examiner has speculated that although Cohen *et al.* do not specify the length of time of the calcium ionophore treatment, nor when the treated monocytes were used after calcium ionophore in Example 2, the fact that "the treated monocytes taught by Cohen could reduce prostate tumor size" (citing to column 12, Example 2) indicates that the treated monocytes taught by Cohen *et al.* have not transformed into mature dendritic cells and are able to activate T cells specific to a prostate antigen, resulting in killing prostate tumor cells.

Applicants must again strongly disagree with the Examiner's summary of Cohen *et al.* and with the Examiner's conclusions as to what the skilled artisan would have "known" at the time of the present invention. Initially, Applicants respectfully remind the Examiner that Koski *et al.* has a publication date of 1999 well after the date of the present invention. Therefore, prior to the Koski *et al.* publication the skilled artisan was unaware of the Examiner's speculated "preferred" window for exposing calcium ionophore treated monocytes to an antigen.

The skilled artisan was taught by Cohen *et al.* that the time period for treating monocytes was a 24 to 48 hour incubation with the calcium ionophore for conversion of the cells into "activated" dendritic cells. Looking to the Cohen *et al.* publication, the Examiner is respectfully directed to column 10, lines 30-32 wherein Cohen *et al.* state one of the goals of their invention is to provide for "conversion of the large monocyte population to an activated DC-like phenotype so that they also can participate in effective antigen processing and presentation." (emphasis added). Further, in column 10, at lines 40-46, Cohen *et al.* describing the use of calcium ionophore to convert monocytes into activated dendritic cells state "adding the calcium ionophore A23187, for example, at the beginning of a 24-48 hr culture period resulted in uniform

activation and dendritic cell phenotypic conversion of the pooled 'monocyte plus DC' fractions . . . ." Therefore, Cohen *et al.* taught the skilled artisan to convert monocytes to an "activated DC-like phenotype" so that the cells can participate in "effective antigen processing and presentation." Further, contrary to the opinion of the Examiner, Cohen *et al.* explicitly taught a time period of 24 to 48 hours for contact of the cells with ionophore, not the shorter "preferred" time period the Examiner has attributed to the skilled artisan based on information provided by Koski *et al.* subsequent to the filing date of the present application.

In addition, Example 2, as noted by the Examiner, does not explicitly state a particular time for culturing the monocytes with calcium ionophore. However, the example does state at column 10, lines 21 and 22 that the dendritic cell enriched fractions "are subject to activation by 500 ng calcium ionophore A23187." (emphasis added). Activation as described by Cohen *et al.* requires a culture period of 24 to 48 hours and conversion to a "DC-like phenotype." These cells as determined by later studies and contrary to the expectations of Cohen *et al.* are actually mature dendritic cells and can not efficiently take up and process antigen.

Applicants also again strongly object to the Examiner's use of Example 2 as an alleged definitive demonstration that patients have been successfully treated by the disclosed method. The statements by Cohen *et al.* regarding the outcome of use of their method as set forth in Example 2 in treating prostate cancer patients are merely speculative. Example 2 must be considered prophetic as no data is provided and the example is presented in the future tense indicating an intension to carry out the described method subsequent to the filing of the application. Also, to the best of Applicants' knowledge data using the method as disclosed by Cohen *et al.* has never been published demonstrating the successful reduction in the size of a prostate tumor in a human patient. It is the belief of Applicants as set forth above that the method of Cohen *et al.* would not result in the successful processing of an antigen because the "activated" dendritic cells described by Cohen *et al.* are mature dendritic cells that can not efficiently process

Applicant has not tested Cohen composition

antigen. The Koski *et al.* reference was provided to the Examiner prior to the interview to support Applicants view of the speculative nature of Example 2.

In view of the remarks above Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 23, 24, and 31-36 under 35 U.S.C. § 102(a) as being anticipated by Cohen *et al.* Should the Examiner continue to reject the claims in view of Cohen *et al.*, Applicants respectfully request an opportunity to discuss the reference with the Examiner, her supervisor, and any technical adviser in order to clarify any remaining issues.

Rejections Under 35 U.S.C. § 103:

Claim 26 remains rejected under 35 U.S.C. § 103 as unpatentable over Cohen *et al.* in view of Lutz *et al.* for the reasons already of record. Briefly, the Examiner believes that the dendritic cells taught by Cohen *et al.* are the same as those presently claimed. Lutz *et al.* is believed by the Examiner to teach making immortalized dendritic cells to allow for their *in vitro* culture for long periods of time.

Applicants must again traverse this rejection. As above, Cohen *et al.* do not claim dendritic cells that are not patentably distinct for the dendritic cells of the present invention. Therefore, Lutz *et al.* adds nothing to render obvious the immortalized dendritic cells, *i.e.*, expanded life span or immortalized dendritic cells, of the present invention. It is respectfully requested that the Examiner reconsider and withdraw this rejection.

Claims 28 and 29 remain rejected under 35 U.S.C. § 103 as allegedly obvious over Cohen *et al.* in view of Taylor *et al.*, because the Examiner believes that it would be obvious to use the cryopreservation techniques of Taylor *et al.* to preserve the dendritic cells of Cohen *et al.* Further, the Examiner believes that one of ordinary skill in the art would have expected that the dendritic cells would have remained functional following cryopreservation.

Applicants respectfully must again traverse this rejection. As above, the dendritic cell populations of the present invention are not the same as those described in

Cohen *et al.* and are therefore patentably distinct. Claims 28 and 29, depend from the dendritic cell population of claim 23, and as claim 23 is patentably distinct from the Cohen *et al.* reference Taylor *et al.* can not provide sufficient guidance or motivation to render obvious claims 28 and 29. It is respectfully requested that the Examiner reconsider and withdraw the rejections of claims 28 and 29 under 35 U.S.C. § 103 as obvious over Cohen *et al.* in view of Taylor *et al.* in light of the above remarks.

Claim 30 remains rejected under 35 U.S.C. § 103 as being obvious over Cohen *et al.* in view of Taylor *et al.* and further in view of Lutz *et al.* for the reason already of record. As above, claim 30 stands rejected because the Examiner believes that the dendritic cell populations of claim 23 are not patentably distinct over Cohen *et al.* and that although Cohen *et al.* do not disclose or suggest immortalized dendritic cells the motivation to combine Taylor *et al.* and Lutz *et al.* with Cohen *et al.* is obvious.

Again, as above, Applicants believe that they have demonstrated that the dendritic cell populations of claim 23 are patentably distinct from those disclosed or suggested by Cohen *et al.* The "activated" dendritic cells that are the goal of the Cohen *et al.* method do not efficiently process antigen as was expected by the inventors. Later work carried out by the Cohen laboratory, including the work of Koski *et al.* discussed above published subsequent to the filing date of the present application, demonstrate that this expectation was not fulfilled by the disclosed methods. Applicants have conclusively demonstrated that the dendritic cell populations of the present invention are patentably distinct from Cohen *et al.*, therefore Taylor *et al.* and Lutz *et al.* can not provide the disclosure and motivation for the use of immortalized dendritic cells of the present invention. Applicants respectfully request that the Examiner reconsider and withdraw the present rejection of claim 30 under 35 U.S.C. § 103 over Cohen *et al.* in view of Taylor *et al.* and further in view of Lutz *et al.*

Claim 37 remains rejected under 35 U.S.C. § 103 as being obvious over Cohen *et al.* in view of Stites *et al.* for the reasons of record. The Examiner continues to believe that as the dendritic cell populations of the present invention are not patentably distinct over those disclosed by Cohen *et al.* as set forth above. Further, the Examiner

believes that Stites *et al.* teach the matching of HLA antigens as important and that it would have been obvious to one of skill in the art at the time of the present invention was made to match HLA of dendritic cells of a donor for a recipient with a reasonable expectation of success.

Again, as with the other claims dependent from the dendritic cell populations of claim 23, claim 37 is not obvious over Cohen *et al.* in view of Stites *et al.* The dendritic cell populations of the present invention are patentably distinct over those disclosed or suggested by Cohen *et al.* Therefore, no motivation is provided to combine the references to render obvious the invention of claim 37. Applicants respectfully request the Examiner reconsider and withdraw the rejection of claim 37 under 35 U.S.C. § 103 over Cohen *et al.* in view of Stites *et al.*

Applicants believe the claims pending in the present application are not obvious over any of the cited art either individually or in any combination as set forth by the Examiner. It is respectfully requested that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §103 in view of the remarks above. Applicants do not believe that Cohen *et al.* discloses or suggests the dendritic cell populations of the present invention and that the dendritic cell populations that are disclosed by Cohen *et al.* are unable to efficiently process an antigen. The dendritic cell population produced would not contain the increased number of human dendritic cells competent and able to activate T cells specific to a prostate antigen as provided by the present invention. Should the Examiner sustain the rejection, Applicants respectfully request they be allowed an interview with the Examiner, her supervisor and any technical advisor with knowledge of the application in order to fully discuss the cited references and rejections.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a

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telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 5 December 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

23. (Five Times Amended) A composition comprising [a] an isolated cell population exposed *in vitro* to a soluble prostate antigen, the cell population having an increased number of human dendritic cells competent and able to activate T cells specific to a prostate antigen as compared to [a] an isolated cell population [directly isolated from peripheral blood] , comprising the same number of dendritic cells, that has not been exposed *in vitro* to the prostate antigen.

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